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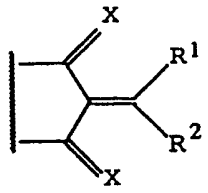
(54) Title: PROTECTING AND LINKING GROUPS FOR ORGANIC SYNTHESIS

(57) Abstract

This invention relates to methods for synthesis of organic compounds, and in particular to compounds useful as protecting and linking groups for use in the synthesis of peptides, oligosaccharides, glycopeptides and glycolipids. The invention provides protecting and linking groups which are useful in both solid phase and solution synthesis, and are particularly applicable to combinatorial synthesis. In its most general aspect, the invention provides a cyclic compound of general formula (I).



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PROTECTING AND LINKING GROUPS FOR ORGANIC SYNTHESIS

This invention relates to methods for synthesis of organic compounds, and in particular to compounds useful as protecting and linking groups for use in the synthesis of peptides, oligosaccharides, glycopeptides and glycolipids. The invention provides protecting and linking groups which are useful in both solid phase and solution synthesis, and are particularly applicable to combinatorial synthesis.

BACKGROUND OF THE INVENTION

The problem of functional group incompatibility in the synthesis of complex organic structures demands the use of a functional group protection strategy. Complex synthetic intermediates and products usually contain a multiplicity of reactive groups, most of which must first be blocked, and subsequently liberated at an appropriate point in the synthesis. The problem is especially acute in the design and construction of polyfunctional molecules such as oligosaccharides, peptides, glycopeptides and glycolipids.

In oligosaccharide synthesis, a variety of protective groups are required. It is necessary to place groups regioselectively at specific locations; on primary alcohols, on cis-diols, on trans-diols, on 1,2-diols, on 1,3-diols, or on particular secondary alcohols. In addition, aminosugars are important constituents of oligosaccharides, and their amino-protection should be compatible with the hydroxy group protection strategy. The properties of the protective group adjacent to the anomeric centre are also important. Whether this group is participating or non-participating plays a significant role in control of glycoside stereochemistry. Because most reactions at the glycosidic centre proceed via electron deficient intermediates, electron-releasing substituents on the C-2 substituent accelerate the reaction at the

glycosidic centre. Electron-withdrawing substituents, normally esters or amides, slow the reaction. In solid phase oligosaccharide synthesis, the stability and sensitivity of the linker between the first sugar unit and the resin becomes a crucial part of the protection plan. The presence of other functional groups, such as alkenes or esters, or features such as a furanose ring in the target oligosaccharide, may dictate that the protecting groups used for the synthesis are not sensitive to acid, base, reductive, or other commonly used cleavage techniques. The choice of protecting groups is therefore one of the decisive factors in the successful realization of solid phase oligosaccharide synthesis.

In solid phase peptide and glycopeptide synthesis the demand of a new orthogonal protective set is significant. The established orthogonal deprotection sets are based upon the well-known Fmoc and Boc protection of amino acids. The construction of complex peptides or glycopeptides often requires a third orthogonal protecting group for side-chain amino functionalities, whose removal will not affect the protecting groups in the other orthogonal sets, or *vice versa*.

Many protecting groups have been developed for amino group protection, and fall into seven broad classes.

1. N-Acyl Derivatives

a) Phthalimides are especially useful in the protection of amino functions in aminoglycoside synthesis (Nicolaou *et al*, 1992), because they are stable during the glycosylation, and because they help to control the stereochemistry by neighbouring group participation. Unfortunately, the deprotection needs vigorous conditions, which often results in partial product decomposition.

b) Trifluoroacetamides (Weygand and Czendes, 1952) Simple amide derivatives are usually worthless as protecting groups because the conditions required to remove them are too harsh. However, the trifluoroacetamide group

is exceptionally labile to base hydrolysis, and is therefore useful in the protection of amines.

c) Carbamates are used as protective groups for amino acids to minimize racemization in peptide synthesis. Racemization occurs during the base-catalysed coupling reaction of an N-protected, carboxyl-activated amino acid, and takes place via the intermediate oxazolone that forms readily from an N-acyl protected amino acid. Many carbamates, for example Boc (McKay and Albertson, 1957), Cbz (Bergman and Zervas, 1932), Alloc (Kunz and Unverzagt, 1984), Teoc (Carpino *et al*, 1978), and Troc (Windholz and Johnston, 1967), have been used as protective groups for amino protection.

2. N-Sulfonyl derivatives

Sulfonamide derivatives are frequently used in nitrogen heterocycles (Gribble *et al*, 1992), and arylsulfonyl (Fischer and Livschitz, 1915) groups are effective protective groups for a wide range of primary and secondary amines, but their deprotection requires drastic conditions. β-(Trimethylsilyl)ethanesulfonyl (Weinreb *et al*, 1986) derivatives are as stable as arylsulfonyl groups, but the cleavage step requires only gentle warming with TBAF or CsF.

3. N-Sulfenyl derivatives

Sulfenamides are much more labile than sulfonamides, being sensitive to acids as well as to attack by nucleophiles. Their deprotection requires exceptionally mild conditions. Several sulfenyl groups are used for the protection of the amino function including tritylsulfenyl (Brandchaud, 1983), o-nitrophenylsulfenyl (Goerdeler and Holst, 1959), and pentachlorphenylsulfenyl (Kessler and Iselin, 1966).

4. N-Alkyl derivatives

Benzylamines give useful protection in reactions in which metal hydrides are used and the carbamates are not stable. Benzylamines are less susceptible to catalytic hydrogenolysis than benzyl ethers or benzyl esters, and thus selective deprotection can often be achieved (Goldstein *et al*, 1992). The trityl group (Sieber and Riniker, 1991) is used to protect amino acids, although its steric bulk and high acid lability is detrimental to peptide coupling. The 9-phenylfluorenyl (PhFl; Koskinen and Rapoport, 1989) group is used for the protection of primary and secondary amines. Its hydrophobicity, steric bulk and ease of introduction are similar to the trityl group, but the PhFl group is about 6000 times more stable to acid than the trityl group.

5. N-Silyl derivatives

The high acid and moisture sensitivity of silylamines has been a major obstacle to their use in amino group protection. Butyldiphenylsilylamines (Overman and Okazaki, 1986) have remarkable stability towards strong basic conditions, but they are still very acid labile.

6. Imine derivatives

The double bond of the imine function allows for the simultaneous protection of both N-H bonds of a primary amine. Imines are generally stable towards strongly basic conditions, but they are labile to aqueous acid. N-Silyl imines (Colvin *et al*, 1988), N-bis(methylthio)methylene-amines (Hoppe and Beckmann, 1979) and N-diphenylmethyleneamines (Polt *et al*, 1979) are valuable for the protection of amino groups in the synthesis of α-amino acids.

7. Enamine derivatives

N-(5,5-Dimethyl-3-oxo-1-cyclohexenyl)amine (Halpern and James, 1964) is used to protect amino acids, giving vinylogous amide derivatives. These compounds can

be cleaved by treatment with either aqueous bromine or nitrous acid. The stability of the vinylogous amide-protected primary amines mainly depends on the structure of 1,3-dione and the functional group attached to the enamine double bond. The open chain N-(4-oxopent-2-enyl)-protected amines are labile towards aqueous and mildly acidic conditions. This acid sensitivity limits their use as synthetic reagents (Kellam, 1996). The cyclic 1,3-diketone, 5,5-dimethylcyclohexane-1,3-dione (dimedone) reacts with dimethylformamide dimethylacetal affording 5,5-dimethyl-2-(dimethylaminomethylene)cyclohexane-1,3-dione. Bycroft *et al* (1993) used this reagent to synthesise Dmc-protected α-amino acids, and found remarkable stability towards acidic conditions. The deprotection of these compounds could be rapidly achieved by a dilute hydrazine solution at room temperature. The introduction of a methyl group to the enamine double bond provided the N-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl Dde-protective group, improving the stability towards secondary amines (Bycroft *et al*, 1993). The N-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl-protected amino acids (Chan *et al*, 1995), carrying a bulkier group at the enamine double bond, had excellent base stability. N-1-(4-Nitro-1,3-dioxoindan-2-ylidene)-ethyl (Nde; Kellam, 1996; Mosher and Meier, 1970) protection of amino acids gave similar vinylogous systems, and deprotection of these could be achieved in very mild conditions.

For many years chemists have attempted to transpose the solid-phase methodology which is routinely used for peptide synthesis to oligosaccharide synthesis, with varying degrees of success. The first attempt was approximately 25 years ago (Frechet and Schuerch, 1971; Frechet and Schuerch, 1972; Guthrie *et al*, 1971; Guthrie *et al*, 1973). However, the ozone-mediated deprotection product was an aldehyde-substituted glycoside. Danishefsky and coworkers described the solid phase synthesis of the Lewis b Antigen (Randolph *et al*, 1995) and *N*-linked

glycopeptides (Roberge *et al*, 1995) by initial attachment of the primary sugar unit of the oligosaccharide to a 1% divinylbenzene-styrene co-polymer support *via* a silyl ether linkage. The resin-bound sugar moiety was in this instance a glycal, with on-resin activation achieved via epoxidation of the double bond, and the resulting glycal residue acting as a sugar donor through nucleophile ring-opening of the epoxide. Since there are no colorimetric methods available to the sugar chemist to monitor on-resin glycosylations, the only means of assessing the progress of the reaction is by lysis of the oligosaccharide-resin bond and subsequent analysis of the cleavage product, usually by thin layer chromatography. The tetra-n-butylammonium fluoride-mediated deprotection conditions required to cleave Danishefsky's silyl ether linker are both hazardous and slow. This, coupled with the requirement for on-resin activation of the tethered glycals, makes the overall strategy and methodology far from ideal.

In an alternative approach, Douglas and coworkers described the synthesis of D-mannopentose using a polyethyleneglycol w-monomethylether co-polymer and a succinoyl or an α,α'-dioxyxylyl diether linker (Douglas *et al*, 1995). The reactions were carried out in solution phase, with removal of unused reactants being achieved by precipitation of the oligosaccharide-polymer complex and subsequent washing. In the latter example, cleavage of the oligosaccharide-polymer bond was achieved through catalytic hydrogenation, which required exposure of the conjugate to 1 atm of H_2 for 48 h to achieve respectable yields. This again is far too slow to allow effective monitoring of individual glycosylation reactions. Yan *et al* reported sulphoxide-mediated glycosylation on a Merrifield resin, using a thiophenol linker for the attachment of the primary sugar residue (Yan *et al*, 1994). This method resulted in the construction of (1-6)-linked oligosaccharides, and was suitable for synthesis of both α- and β-glycosidic linkages. However, the thioglycosidic linkage to the resin

dictates that similar sugar donors cannot be employed in this strategy.

Recently Rademann and Schmidt reported the use of trichloroacetimidate sugar donors to a resin bound sugar tethered *via* an alkyl thiol (Rademann and Schmidt, 1996); once again, however, this method precludes the use of the far superior thioglycoside sugar donors. Meanwhile, Adinolfi *et al* described the synthesis of disaccharides using a polyethyleneglycol-polystyrene resin, with connection of the first sugar to the polymeric support through a succinate spacer (Adinolfi *et al*, 1996). However, the acid lability displayed by this linker means that the primary sugar cannot be linked to the resin *via* the glycosidic position.

These examples illustrate that the critical element in solid phase synthesis is the nature of the linker between the solid support and the initial synthon. The linker must display excellent stability to the conditions of coupling and deprotection, yet in the case of solid phase oligosaccharide synthesis, it should also be rapidly and efficiently cleaved to allow monitoring of the progress of individual coupling reactions. The cleavage should ideally be achieved by the use of a relatively innocuous chemical reagent. There remains a need in the art for simple, efficient and economical methods for solid-phase synthesis of oligosaccharides.

In our International Patent Application No. PCT/AU97/00544 (priority date 28 August 1996), we have shown several ways of immobilizing 2-acyl-5,5-dimethyl-1,3-cyclohexanedione and of utilizing the immobilized compound in solid phase oligosaccharide synthesis. In our International Patent Application No. PCT/AU98/00131 (priority date 28 February 1997), we have shown that vinylogous amide protection of aminosugars could be achieved in simple reactions using Dde-OH and Nde-OH reagents. The entire disclosures of these specifications are incorporated herein by this reference. The Dde- and

Nde-protected monosaccharides survived most of the hydroxyl protective group manipulations and the reactions which occurred at the glycosidic center, affording a wide variety of sugar donors. These vinylogous amide-protected aminosugar donors were not neighbouring group active carbohydrates, giving anomeric mixtures of glycosides during the glycosylations. We have demonstrated the stability and the ease of deprotection of the Dde- and Nde-protected aminosugars in carbohydrate-based methodology.

Unfortunately even these protective strategies still present some difficulties.

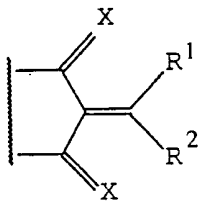
The Dde-protected aminosugars are not stable in the presence of sodium cyanoborohydride and metal hydrides. These reagents are often used in benzylidene ring opening reactions and during benzyl protection of hydroxyl groups. This hydride sensitivity of the Dde group limits its application in carbohydrate chemistry. The preparation of 2-acyl-dimedones is very often difficult. One of the major side reactions is O-acylation, which lowers the overall yields and causes difficult chromatographic purification problems.

Nde-protection of primary amines always gives a mixture of E/Z isomers which may not be separable, causing difficult characterisation problems. The formation of 2-acetyl-4-nitroindan-1,3-dione involves the reaction between 4-nitrophthalic anhydride and 2,4-pentanedione via a condensation and two rearrangements. This synthetic strategy does not give an opportunity to prepare Nde-OH analogues.

We have now synthesized a family of novel compounds useful as protecting and linking groups for organic synthesis.

SUMMARY OF THE INVENTION

In its most general aspect, the invention provides a cyclic compound of general formula I



I

wherein the ring is a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, saturated bicyclo[p, q, r], substituted saturated bicyclo[p, q, r], saturated heterobicyclo[p, q, r], substituted saturated heterobicyclo[p, q, r], unsaturated bicyclo[p, q, r], substituted unsaturated bicyclo[p, q, r], unsaturated heterobicyclo[p, q, r], substituted unsaturated heterobicyclo[p, q, r], saturated tricyclo[p, q, r, s], substituted saturated tricyclo[p, q, r, s,], unsaturated tricycloalkyl[p, q, r, s], unsaturated substituted tricycloalkyl[p, q, r, s], saturated heterotricyclo[p, q, r, s,], substituted saturated heterotricyclo[p, q, r, s,], unsaturated heterotricyclo[p, q, r, s,] or substituted unsaturated heterotricyclo[p, q, r, s,] ring system; where p, q, r and s may be the same or different, and each of p, q, r and s is an integer of from 0 to 5;

X is oxygen, sulphur, imino or substituted imino;

R^1 is hydrogen; an alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloheteroaryl, cycloalkyl, heterocycloalkyl, alkanal, or thioalkanal group, each of which may be substituted or unsubstituted; NH_2, guanidino, CN, substituted amino, quaternary ammonium, O^-, formyl, imino or substituted imino, COOH, or a carboxylic acid derivative;

R^2 is an alkylamino, dialkylamino, arylamino, or diarylamino group, each of which may be substituted or unsubstituted; O-substituted hydroxylamino, substituted or unsubstituted hydrazino, substituted or unsubstituted

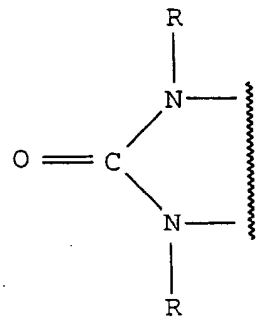
hydrazido, substituted or unsubstituted thiohydrazido, semicarbazido, thiosemicarbazido, OH, O^-M, NH_2, NHOH, SH, S^-M^+, halogen; O-alkyl, O-acyl, O-aryl, alkylthio, S-aryl, acylthio, alkylsulfonyl or arylsulfonyl, each of which may be substituted or unsubstituted; and M is a metal ion, or an organic or inorganic cation such as a quaternary amine group, a trityl group or an ammonium group,

with the proviso that the compound is not one disclosed in International Patent Application No. PCT/AU97/00544.

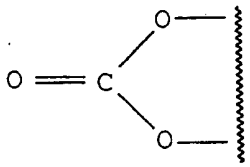
A wide variety of suitable cations is known in the art. The metal ion can be mono- or multivalent, and may form a complex salt.

Preferably the ring is 4- to 8-membered cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

Alternatively in other preferred forms, the ring is a 5- to 8-membered ring of the lactone or lactam type, or a 6- to 8-membered ring of the carbamido or substituted carbamido type, as follows:



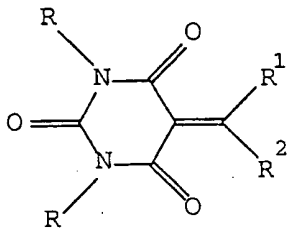
in which each R is independently H, substituted or unsubstituted alkyl, aryl, alkenyl, alkynyl or acyl, or may be a 6- to 8-membered ring of the carbonate type, as follows:



It will be clearly understood that in the general formulae of this specification, each of the substituent groups R, R^1, R^2 and R^3 may itself be substituted, *ie.* one or more hydrogen atoms may be replaced by a substituent group.

For the purposes of this specification the term "substituted" in the definitions of R, R^1 and R^2, and in definitions of other substituents within this specification, means that the substituent is itself substituted with a group which modifies the general chemical characteristics of the chain. Preferred substituents include but are not limited to halogen, nitro, amino, azido, oxo, hydroxyl, thiol, carboxy, carboxy ester, carboxyamide, alkylamino, alkyldithio, alkylthio, alkoxy, acylamido, acyloxy, or acylthio, each of 1 to 3 carbon atoms. Such substituents can be used to modify characteristics of the molecule as a whole, such as stability, solubility, and ability to form crystals. The person skilled in the art will be aware of other suitable substituents of similar size and charge characteristics which could be used as alternatives in a given situation.

In one group of preferred embodiments, the compound is of general formula II



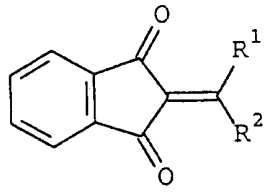
II

in which each R is independently H or a substituted or unsubstituted alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or heterocycloalkyl; and

R^1 and R^2 are as defined in general formula I.

Preferably each R has 1 to 6, more preferably 1 to 4 carbon atoms.

In another group of preferred embodiments, the compound is of general formula III



III

in which

R^1 and R^2 are as defined in general formula I.

The compounds of the invention are useful in a wide variety of areas of organic chemistry. The compounds are especially useful in the solution and/or solid phase synthesis of oligosaccharides and peptides. Uses of the compounds of the invention thus include but are not limited to the following:

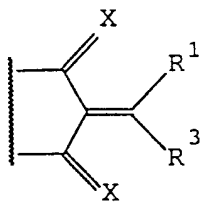
1. Linker groups for solid-phase oligosaccharide synthesis;
2. N-protecting groups for protection of amino sugars in oligosaccharide synthesis;
3. Linker groups for solid phase organic synthesis;
4. N-protecting groups for organic synthesis;
5. N-side chain and/or N_α protecting groups for solid or solution phase peptide synthesis;
6. Amino protecting groups for sugars, peptides and organic compounds, affording an additional free enamine;

7. Certain compounds of the invention are chiral; these are useful in resolution of enantiomers and in stereospecific synthesis.

8. Linker groups for coupling of a starter group to a resin for solid phase synthesis of oligosaccharides, peptides and other organic compounds.

Thus in a second aspect, the invention provides an N-protecting group for oligosaccharides, amino acids, peptides or organic compounds.

An example of the application of this group for the protection of amino groups during oligosaccharide synthesis is shown in general formula IV

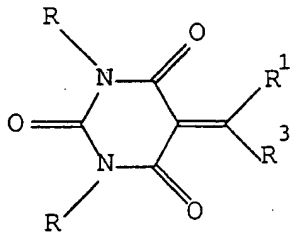


IV

wherein the ring, X and R^1 are as defined in general formula I, and

R^3 is a protected, unprotected or substituted sugar amino-, a glycosylamino-, or a glycosylamino group of an oligosaccharide; or a mono- or oligosaccharide coupled through a substituted or unsubstituted alkylamino-, arylamino-, cycloalkylamino, heteroalkylamino, heteroarylamino or heterocycloalkylamino group.

In one group of preferred embodiments, the compound is of general formula V



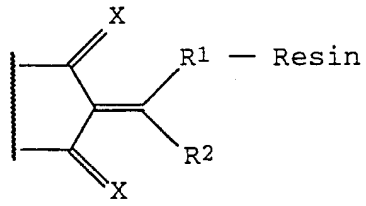
V

in which R and R^1 are as defined in general formula II, and R^3 is as defined in general formula IV.

Preferably R^3 is a protected, unprotected or substituted sugar amino-, a glycosylamino-, or a glycosylamino group of an oligosaccharide.

Alternatively, R^3 is an oligosaccharide-O-CH_2-(C_6H_4)-NH-, monosaccharide-O-CH_2-(C_6H_4)-NH-, oligosaccharide-CO_2CH_2-(C_6H_4)NH-, or monosaccharide-CO_2CH_2-(C_6H_4)-NH group.

In a third aspect the invention provides a support of general formula VI for solid-phase synthesis of oligosaccharides, peptides or organic compounds, comprising a resin and a linker covalently attached to the resin:



VI

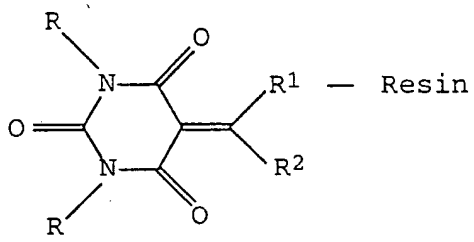
wherein the ring, X and R^2 are as defined in general formula I, and

R^1 is a substituted or unsubstituted alkyl, cycloalkyl, heteroalkyl, heteroaryl, heterocycloalkyl or carboxylamido spacer group which is directly coupled to the resin support, or which may optionally be coupled to the resin support via a suitable covalent linkage, which is

stable to conditions of oligosaccharide synthesis and cleavage.

The covalent linkage may suitably be provided by a -CONH-, -O-, -S-, -NH-, -COO-, -COS-, -CH=N-, -NHCONH-, -NHCSNH, -NHNH- grouping, *eg.* Spacer-CONH-resin, Spacer-O-resin, Spacer-S-resin, Spacer-S-S-resin, Spacer-CO_2-resin, Spacer-CH=N-resin, Spacer-NHCONH-resin, Spacer-NHCSNH-resin, Spacer-NHNH-resin. Other possible covalent linking groups will be known to those skilled in the art.

In a particularly preferred embodiment, the linker is a barbituric acid of general formula VII



VII

in which R and R^2 are as defined in general formula I, and R^1 is as defined in general formula VI,

in which a compound of general formula II is directly coupled to the resin support, or may optionally be coupled to the resin support via a suitable covalent linkage which is stable to conditions of oligosaccharide synthesis and cleavage.

The covalent linkage may suitably be provided by a -CONH-, -O-, -S-, -NH-, -COO-, -COS-, -CH=N-, -NHCONH-, -NHCSNH, or -NHNH- grouping, *eg.* Spacer-CONH-resin, Spacer-O-resin, Spacer-S-resin, Spacer-S-S-resin, Spacer-CO_2-resin, Spacer-CH=N-resin, Spacer-NHCONH-resin, Spacer-NHCSNH-resin, Spacer-NHNH-resin. Other possible covalent linking groups will be known to those skilled in the art.

The resin may be any resin which swells in water and/or in an organic solvent, and which comprises one of

the following substituents: halogen, hydroxy, carboxyl, SH, NH_2, formyl, SO_2NH_2, or $NHNH_2$, for example methylbenzhydrylamine (MBHA) resin, amino or carboxy tentagel resins, or 4-sulphamylbenzyl AM resin. Other suitable resins will be known to those skilled in the art. Alternatively, supports such as controlled-pore glass or soluble polymer supports may be used. These are well known in the art.

The invention also provides a method of solid-phase synthesis of oligosaccharides, comprising the step of sequentially linking mono- or oligosaccharide groups to a support as described above.

The linker may be synthesised directly on the resin in a stepwise manner prior to the coupling of the initial sugar group, or the linker-initial sugar conjugate may be synthesised in solution phase and subsequently coupled to the solid support, with subsequent sugars being sequentially attached. Preferably the second and all subsequent sugar groups are coupled to the oligosaccharide chain-resin conjugate after the last sugar in the oligosaccharide chain is partially deprotected.

The first sugars attached to the resin-linker unit may be unprotected, partially protected or fully protected glycosides, aminoglycosides, or ether- or amino-linked sugars.

Preferably the first sugar coupled to the resin is an aminosugar, an aminoglycoside or an amino-oligosaccharide, or a glycosyl amines of an oligosaccharide.

In one particularly preferred embodiment the support comprises a resin, a linker and a saccharide selected from the group consisting of monosaccharide, oligosaccharides, or aminosaccharides and aminooligosaccharides.

The building block mono- or oligosaccharide-donors may be any activated sugar, including but not limited to orthoesters, thio-orthoesters, cyanoalkylidene

derivatives, 1-*O*-acyl sugars, amino sugars, acetimidates, trichloroacetimidates, thioglycosides, aminoglycosides, aminoligosaccharides, glycosylamines of oligosaccharides, glycosyl thiocyanates, pentenyl glycosides, pentenoylglycosides, isopropenyl glycosides, glycals, tetramethylphosphoro diamidates, sugar diazirines, selenoglycosides, phosphorodithioates, glycosyl-dialkylphosphites, glycosylsulphoxides and glycosylfluorides.

Preferably partial sugar deprotection is achieved by using acyl-type, trityl, methoxytrityl, methoxybenzyl, various silyl and/or photolabile protecting groups in addition to permanent ether-type protecting groups. This permits the synthesis of branched oligosaccharides by using two orthogonal hydroxy-protecting groups on a single sugar donor.

The synthesised oligosaccharide can be cleaved from the resin using ammonia, hydrazine or a primary amine, such as butylamine or cyclohexylamine. For the preparation of aminoglycosides, ammonia or a suitable primary amine in an organic solvent is preferably employed. For the preparation of hydrazides, hydrazine in water or an organic solvent is preferably employed. For the preparation of oligosaccharides, ammonia in water or organic solvent is preferably employed, followed by acidification. When the linker contains a 4-aminobenzyl moiety, after cleavage as described above the first sugar is released still protected by the aminobenzyl group; this can be removed by hydrogenation if desired.

In a preferred embodiment, the invention provides a reagent for solution phase synthesis of sugar-containing compounds, comprising a barbituric acid derivative compound of general formula II as defined above.

The compounds of the invention are suitable for use as protecting groups in methods of solid-phase oligosaccharide synthesis, in which sugar units are linked to a resin. Any suitable linker compound may be used,

including compounds of the invention. It is contemplated that linkers and methods described in our earlier application, PCT/AU97/00544, are also suitable for use with the compounds of this invention.

Thus in a fourth aspect the invention provides a linker-saccharide complex, comprising a linker group and a starting compound comprising a protecting group of general formula I or II as defined above. Any suitable linker may be used, including the compounds of the invention. Again, it is contemplated that linkers and methods described in PCT/AU95/00544 may be used.

In a fifth aspect the invention provides a method of solution phase synthesis of oligosaccharides, comprising the step of sequentially linking mono- or oligosaccharide groups to a linker-saccharide complex as described above.

These methods are particularly useful for combinatorial synthetic applications. The solution phase method of the invention may, for example, be used for combinatorial synthesis of aminoglycoside compounds.

The invention also provides kits useful in solution phase synthesis or combinatorial synthesis of oligosaccharides or peptides, comprising either

a) a resin-linker-saccharide or resin-linker-peptide (or amino acid) support,

b) a linker-saccharide or linker-peptide (or amino acid) complex, or

c) a resin-linker support,

according to the invention, as described above.

For peptide synthesis it may be convenient in some circumstances to start with a resin-linker-amino acid support or linker-amino acid complex, while in others a starter peptide may more suitably be provided in the support or linker complex. The kit may optionally also comprise one or more further reagents such as protecting agents, deprotecting agents, and/or solvents suitable for solid phase or combinatorial synthesis. The person skilled in the art will be aware of suitable further reagents.

Different types of kit can then be chosen according to the desired use.

The invention also provides a kit useful in solid phase synthesis or combinatorial synthesis of oligosaccharides, comprising a linker-saccharide complex according to the invention, as described above. The kit may optionally also comprise one or more further reagents such as protecting agents, deprotecting agents, and/or solvents suitable for solid phase or combinatorial synthesis. The person skilled in the art will be aware of suitable further reagents. Different types of kit can then be chosen according to the desired use.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

Detailed Description of the Invention

Abbreviations used herein are as follows:

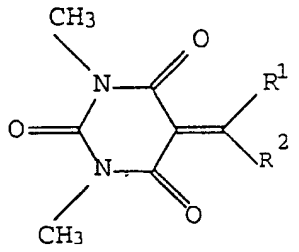
Ac	Acetyl
AcOH	Acetic acid
ADA	5-Acyl-1,3-dimethylbarbituric acid
Alloc	Allyloxycarbonyl
Boc	tert-Butoxycarbonyl
Bu	butyl
Cbz	Benzyloxycarbonyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
Dde	N-1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-ethyl
DMAP	4-Dimethylaminopyridine
Dmc	N-(4,4-Dimethyl-2,6-dioxocyclohexylidene-methylene)
DMF	N,N'-Dimethylformamide
EtOH	Ethanol
FAB MS	Fast atom bombartment mass spectrometry
Fmoc	9-Fluorenylmethoxycarbonyl

MBHA	methylbenzylhydramine
Me	Methyl
MeOH	Methanol
Nde	1-(4-Nitro-1,3-dioxoindan-2-ylidene)ethyl
NMR	Nuclear magnetic resonance
ODmab	-{N-[1-(4,4-dimethyl-2,6-dioxocyclohexyl-idene)-3-methylbutyl]-amino}benzyl alcohol
PhFl	9-Phenylfluorenyl
TBAF	Tetrabutylammonium fluoride
TEAB	Tetraethylammonium bromide
Teoc	2-(Trimethylsilyl)ethoxycarbonyl
TNBS	2,4,6-trinitrobenzene sulphonic acid
Troc	2,2,2-Trichloroethoxycarbonyl

The invention will now be described in detail by way of reference only to the following non-limiting examples, in which the structures of individual compounds are as summarised in the following tables and structures.

Table 1

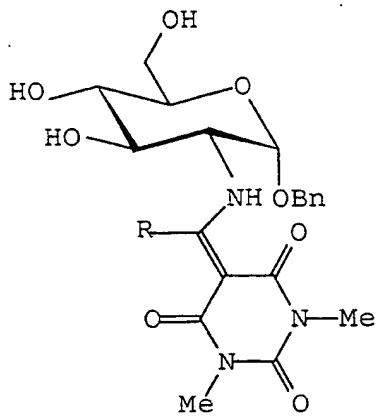
Compounds 1-20



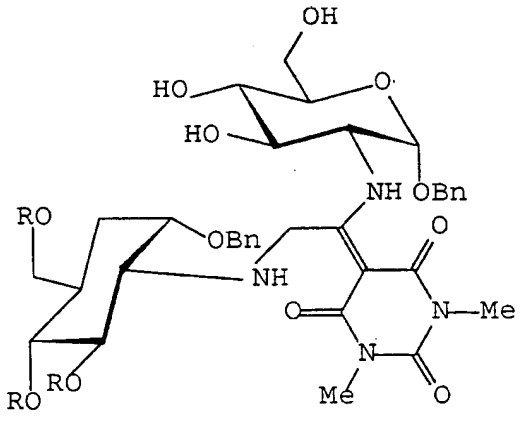
Compound	R^1	R^2
1	OH	CH_3
2	NHBu	CH_3
3	OH	Ph
4	NHBu	Ph
5	OH	9-fluorenyl
6	OH	CH_2Cl
7	OH	$CHCl_2$
8	OH	Bn
9	OH	$CHPh_2$
10	OH	$-(CH_2)_3COOH$
11	OH	t-Bu
12	OH	1-adamantyl
13	NH_2	CCl_3
14	$-NHCH_2COOH$	CH_3
15	$-NHCH_2COOH$	Ph
16	$-NHCH_2COOH$	Bn
17	-NHOH	Ph
18	$-NHNHCOCH_3$	Ph
19	$-NH-NH_2$	Ph
20	NH_2	Ph

Table 2

Compounds 21-29



Compound	R
21	CH_3
22	Ph
23	9-fluorenyl
24	Bn
25	$CHPh_2$
26	$-(CH_2)_3COOH$
27	NH_2
28	t-Bu
29	1-adamantyl



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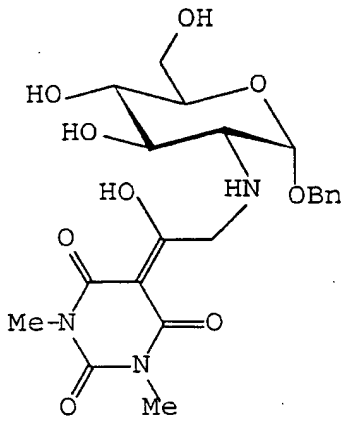

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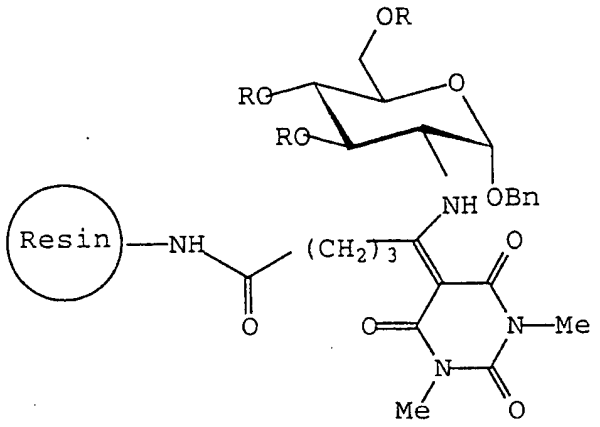
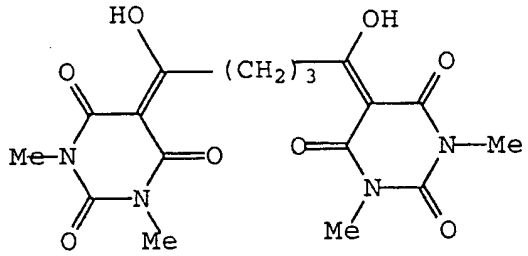


32	R = Ac
37	R = H



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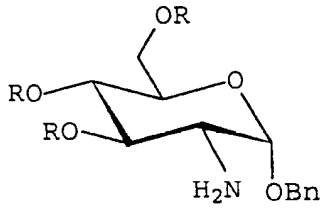

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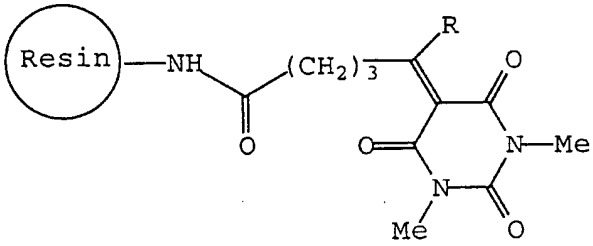
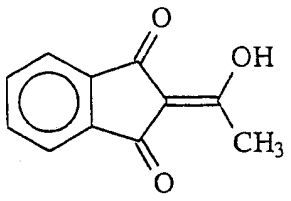


35	R = NH_2
36	R = OH



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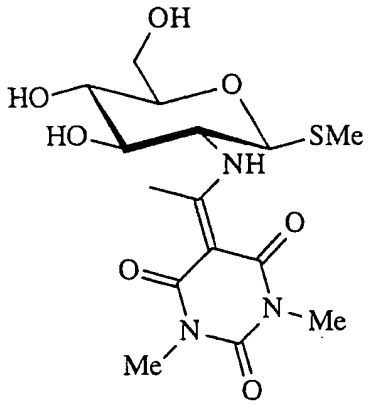

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We have now developed a novel enamine-type protective system, including the preparation of reagents, and methods for selective amino group protection and deprotection. This has been illustrated by synthesizing a number of 5-acyl-1,3-dimethyl-barbituric acids (ADA) (Examples 1-11). During the syntheses only C-acyl products were formed; no O-acylation was observed. The 5-acylation of 1,3-dimethylbarbituric acid was successfully carried out using carboxylic acids in the presence of DCC and DMAP (Examples 5 to 9). The more reactive acyl chlorides (Examples 3 to 4) and anhydrides (Examples 1 to 2) were also used, giving the same products in a DMAP-catalyzed reaction. Trichloroacetonitrile was used to construct a similar structure in the present of DBU (Example 10).

The 5-acyl-1,3-dimethylbarbituric acids were easily crystallized from polar solvents, avoiding the need for chromatographic purifications. These reagents are very cheap and easy to synthesize in a single reaction from the readily available 1,3-dimethyl-barbituric acid. We have used the 5-acyl-1,3-dimethylbarbituric acid reagents to prepare a wide variety of protected primary alkylamines (Examples 12-13), aminosugars (Examples 22 to 28) and amino acids (Examples 14 to 16).

The ADA-protected aminosugars can be used as aminosugar acceptors and aminosugar donors for solid or solution phase oligosaccharide synthesis. The ADA-protected amino acids are particularly useful as reagents for solid-phase peptide and glycopeptide syntheses, because they are unable to form oxazolones during the coupling reactions. Thus, no racemization can occur during the peptide bond formation (racemization can only occur in base-catalyzed proton abstraction). The ADA-protection is ideally orthogonal to the Boc-protection and quasi-orthogonal to the Fmoc system.

We have demonstrated that the system can be used for the protection of hydroxylamines (Example 17), hydrazines (Example 19) and hydrazides (Example 18). The vinylogous amide protection of amino groups was efficiently achieved by simply refluxing the unprotected amines with the precursor (5-acyl-1,3-dimethylbarbituric acid) in abs. EtOH.

The ADA-protected derivatives are very stable in a wide range of reactions and work-up conditions. Different reagents (NH_3, N_2H_4, NH_2OH, n-$BuNH_2$, $BnNH_2$, $NH-NHCOCH_3$, N_2H_4xAcOH, NaOH) have been developed for the cleavage of the protecting groups (Examples 17 to 20). The speed of protection and cleavage depends on the electronic and steric effects of the 5-acyl functional group.

We have also synthesized bifunctional 5-acyl-1,3-dimethylbarbituric acids (Example 11), which can be used as linkers for solid phase organic chemistry. We have successfully immobilized a bifunctional 5-acyl-1,3-dimethylbarbituric acid producing a "resin-linker conjugate" (Example 35). We have proved that this "resin-linker conjugate" was suitable for solid phase oligosaccharide synthesis by immobilizing a monosaccharide (Example 32), deprotecting its hydroxyl groups (Example 33) and later realising it during the cleavage (Example 33). We have demonstrated that the resin-linker conjugate was reusable, regenerating the original hydroxyl function with

aqueous base treatment (Example 36). Alternatively the "amino-substituted resin-linker conjugate" itself may be used for the next immobilization (Example 34).

The introduction of another reactive centre into the protecting group makes the system more flexible. Using 5-chloroacetyl-1,3-dimethylbarbituric acid, we have synthesised a chiral carbohydrate containing reagent (Example 31) for protection of organic compounds bearing an amino functionality. These types of molecules are especially suitable for resolution of enantiomers.

The 5-trichloroacetimino-1,3-dimethyl-barbituric acid gave rare 1,1-elimination in the reaction with primary amines, affording a novel type of compound (Example 29).

Example 1 5-Acetyl-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpc-OH) **1**

A mixture of 1,3-dimethylbarbituric acid (10 g, 64.04 mmol), 4-dimethylaminopyridine (9.49 g, 158.0 mmol) in dry CH_2Cl_2 (190 ml) was cooled to 0°C and acetic anhydride (7.35 ml, 77.9 mmol) added dropwise in 15 min. The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (500 ml) and washed with 2 N HCl solution (80 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallised from MeOH, giving 5-acetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **1** (8.6 g, 68%).

R_f 0.37 (EtOAc/hexane 2:1);
FAB MS $C_8H_{10}N_2O_4$ (198.18) m/z (%) 199 $[M+H]^+$ (100), 183 (18).
^1H NMR ($CDCl_3$) d 17.26 (s, 1H, OH), 3.36, 3.32 (2s, 6H, 2 NCH_3), 2.71 (s, 3H, CH_3).

Example 2 5-Chloroacetyl-1,3-Dimethyl-2,4,5(1H,3H,5H)-Pyrimidinetrione (Dtpc-OH) **6**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.02 mmol), 4-dimethylaminopyridine (9.76 g, 80.05 mmol) in dry CH_2Cl_2 (75 ml) was cooled to 0°C and chloroacetic

anhydride (6.57 g, 38.46 mmol) added. The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (150 ml) and washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallised from MeOH, giving 5-chloroacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **6** (4.57 g, 61%).

R_f 0.41 (hexane/EtOAc/AcOH 10:5:0.1);
FAB MS $C_8H_9ClN_2O_4$ (232.62) m/z (%) 233 $[M+H]^+$ (100), 197 (58), 183 (15).
^1H NMR ($CDCl_3$) d 17.93 (s, 1H, OH), 4.97 (s, 2H, CH_2), 3.41, 3.34 (2s, 6H, 2 NCH_3).

Example 3 5-Benzoyl-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpb-OH) **3**

A mixture of 1,3-dimethylbarbituric acid (5 g, 32.02 mmol), 4-dimethylaminopyridine (4.74 g, 38.79 mmol) in dry CH_2Cl_2 (75 ml) was cooled to 0°C and benzoyl chloride (4.95 g, 35.22 mmol) added dropwise in 15 min. The reaction mixture was stirred for 3 h at room temperature, diluted with CH_2Cl_2 (150 ml) and washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallised from diisopropylether then recrystallised from MeOH, giving 5-benzoyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **3** (5.32 g, 64%).

R_f 0.45 (EtOAc/hexane/TFA 10:15:0.1);
FAB MS $C_{13}H_{12}N_2O_4$ (260.25) m/z (%) 283 $[M+Na]^+$ (25), 261 $[M+H]^+$ (100), 245 (45), 183 (55).
^1H NMR ($CDCl_3$) d 16.58 (s, 1H, OH), 7.57 - 7.45 (m, 5H, 5 Ar-H), 3.44, 3.27 (2s, 6H, 2 NCH_3).

Example 4 5-Pivaloyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (Dtppe-OH) **11**

A mixture of 1,3-dimethylbarbituric acid (5 g, 32.02 mmol), 4-dimethylaminopyridine (4.69 g, 38.42 mmol) in dry CH_2Cl_2 (75 ml) was cooled to 0°C and pivaloyl chloride (4.24 g, 35.22 mmol) added dropwise in 15 min. The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (150 ml) and washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using hexane/EtOAc/AcOH 15:5:0.1 as the mobile phase to give 5-pivaloyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **11** (5.46 g, 71%).

R_f 0.65 (hexane/EtOAc/AcOH 15:5:0.1);
FAB MS $C_{11}H_{16}N_2O_4$ (240.26) m/z (%) 263 $[M+Na]^+$ (7), 241 $[M+H]^+$ (100), 223 (15), 183 (15).
^1H NMR ($CDCl_3$) d 19.14 (s, 1H, OH), 3.38, 3.33 (2s, 6H, 2 NCH_3), 1.41 (s, 9H, 3 CH_3).

Example 5 5-(9-Fluorenylcarbonyl)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpf-OH) **5**

A mixture of 1,3-dimethylbarbituric acid (2.5 g, 16.01 mmol), 9-fluorenylcarboxylic acid (5.05 g, 24.01 mmol), 4-dimethylaminopyridine (0.98 g, 8.00 mmol) in dry CH_2Cl_2 (15 ml) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (3.30 g, 16.01 mmol) added. The reaction mixture was stirred at room temperature overnight and filtered. The solid was washed with CH_2Cl_2 (50 ml) and the combined solution was washed with 2 N HCl solution (5 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallised from recrystallised from MeOH giving 5-(9-fluorenyl-carbonyl)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **5** (2.85 g, 69%).

R_f 0.49 (EtOAc/hexane/TFA 10:25:0.1);

FAB MS $C_{20}H_{16}N_2O_4$ (348.35) m/z (%) 349 $[M+H]^+$ (100), 338 (32), 183 (72), 164 (71).
^1H NMR ($CDCl_3$) d 17.33 (s, 1H, OH), 7.81 (d, 2H, 2 Ar-H), 7.42 (m, 4H, 4 Ar-H), 7.30 (d, 2H, 2 Ar-H), 6.92 (s, 1H, CH), 3.48, 3.40 (2s, 6H, 2 NCH_3).

Example 6 5-Dichloroacetyl-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpd-OH) **7**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.05 mmol), dichloroacetic acid (6.19 g, 48.03 mmol), 4-dimethylaminopyridine (1.95 g, 16.01 mmol) in dry CH_2Cl_2 (30 ml) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (7.26 g, 35.22 mmol) added. The reaction mixture was stirred at room temperature overnight and filtered. The solid was washed with CH_2Cl_2 (150 ml) and the combined solution was washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallised from MeOH giving 5-dichloroacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **7** (5.41 g, 63%).

R_f 0.27 (hexane/EtOAc/AcOH 10:5:0.1);
FAB MS $C_8H_8Cl_2N_2O_4$ (267.07) m/z (%) 289 $[M+Na]^+$ (10), 267 $[M+H]^+$ (100), 231 (66), 197 (33), 183 (24).
^1H NMR ($CDCl_3$) d 17.94 (s, 1H, OH), 7.91 (s, 1H, CH), 3.43, 3.35 (2s, 6H, 2 NCH_3).

Example 7 5-Phenylacetyl-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpp-OH) **8**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.05 mmol), phenylacetic acid (6.53 g, 48.03 mmol), 4-dimethylaminopyridine (1.95 g, 16.01 mmol) in dry CH_2Cl_2 (30 ml) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (7.26 g, 35.22 mmol) added. The reaction mixture was stirred at room temperature overnight and filtered. The solid was washed with CH_2Cl_2 (150 ml) and the combined solution was washed with 2 N HCl solution (40 ml). The

organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallized from MeOH giving 5-phenylacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **8** (6.10 g, 69%).

R_f 0.41 (hexane/EtOAc/AcOH 10:5:0.1);
FAB MS $C_{14}H_{14}N_2O_4$ (274.27) m/z (%) 297 $[M+Na]^+$ (11), 275 $[M+H]^+$ (100), 257 (13), 183 (31).
^1H NMR ($CDCl_3$) d 17.61 (s, 1H, OH), 7.54 - 7.26 (m, 5H, 5 Ar-H), 4.49 (s, 2H, CH_2Ar), 3.38, 3.34 (2s, 6H, 2 NCH_3).

Example 8 5-Diphenylacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (Dtpd-OH) **9**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.05 mmol), diphenylacetic acid (10.19 g, 48.03 mmol), 4-dimethylaminopyridine (1.95 g, 16.01 mmol) in dry CH_2Cl_2 (30 ml) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (7.26 g, 35.22 mmol) added. The reaction mixture was stirred at room temperature overnight and filtered. The solid was washed with CH_2Cl_2 (150 ml) and the combined solution was washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallized from EtOH giving 5-diphenylacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **9** (6.70 g, 59%).

R_f 0.64 (hexane/EtOAc/AcOH 10:5:0.1);
FAB MS $C_{20}H_{18}N_2O_4$ (350.36) m/z (%) 373 $[M+Na]^+$ (8), 351 $[M+H]^+$ (100), 338 (24), 333 (16).
^1H NMR ($CDCl_3$) d 18.28 (s, 1H, OH), 7.32 - 7.27 (m, 10H, 10 Ar-H), 7.02 (s, 1H, $CHAr_2$), 3.36, 3.31 (2s, 6H, 2 NCH_3).

Example 9 5-(1-Adamantanecarbonyl)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpa-OH) **12**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.05 mmol), 1-adamantanecarboxylic acid (8.65 g, 48.03 mmol), 4-dimethylaminopyridine (1.95 g, 16.01 mmol)

in dry CH_2Cl_2 (30 ml) was cooled to 0°C and 1,3-dicyclohexylcarbodiimide (7.26 g, 35.22 mmol) added. The reaction mixture was stirred at room temperature overnight and filtered. The solid was washed with CH_2Cl_2 (150 ml) and the combined solution was washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallized from MeOH giving 5-(1-adamantanecarbonyl)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **12** (7.10 g, 69%).

R_f 0.57 (hexane/EtOAc/AcOH 15:5:0.1);
FAB MS $C_{17}H_{22}N_2O_4$ (318.37) m/z (%) 319 $[M+H]^+$ (100), 301 (33), 223 (13), 183 (94).
^1H NMR ($CDCl_3$) d 19.23 (s, 1H, OH), 3.38, 3.35 (2s, 6H, 2 NCH_3), 2.18, 2.07 (2s, 12H, 6 CH_2), 1.79 (m, 3H, 3 CH).

Example 10 5-Trichloroacetimino-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (Dtpe-NH_2) **13**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.02 mmol), 4-dimethylaminopyridine (1.95 g, 16.01 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene /DBU/ (10 drops) in dry CH_2Cl_2 (50 ml) was cooled to 0°C and trichloroacetonitrile (13.87 g, 96.06 mmol) added dropwise in 15 min. The reaction mixture was stirred at 0°C for 30 min then at room temperature for 3 h, diluted with CH_2Cl_2 (50 ml) and washed with 1 N $KHSO_4$ solution (10 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallized from MeOH giving 5-acetimino-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **13** (6.22 g, 65%).

R_f 0.61 (EtOAc/hexane 1:1);
FAB MS $C_8H_8Cl_3N_3O_3$ (300.53) m/z (%) 322 $[M+Na]^+$ (10), 300 $[M+H]^+$ (100), 264 (43), 243 (17), 207 (11), 183 (17).
^1H NMR ($CDCl_3$) d 13.13, 7.83 (2s, 2H, 2 NH), 3.37, 3.33 (2s, 6H, 2 NCH_3).

Example 11 5-(4-Carboxybutyryl)-1,3-Dimethyl-2,4,6(1H,3H,5H)-Pyrimidinetrione (Dtpp-OH) 10 and 1,5-bis-(1,3-Dimethyl-2,4,6-(1H,3H,5H)-Trioxopyrimidin-5-ylidene)-1,5-Dihydroxy Pentane **33**

A mixture of 1,3-dimethylbarbituric acid (5.00 g, 32.02 mmol), 4-dimethylaminopyridine (9.789 g, 80.05 mmol) in dry CH_2Cl_2 (75 ml) was cooled to 0°C and glutaric anhydride (4.38 g, 38.42 mmol) added. The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (150 ml) and washed with 2 N HCl solution (40 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was crystallized from AcOH giving 1,5-bis-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-1,5-dihydroxy pentane **33** (1.2 g).

R_f 0.71 (CH_2Cl_2/MeOH/AcOH 96:3:1);
FAB MS $C_{17}H_{20}N_4O_8$ (408.36) m/z (%) 431 $[M+Na]^+$ (8), 409 $[M+H]^+$ (100).
^1H NMR ($CDCl_3$) d 17.67 (s, 2H, 2 OH), 3.37, 3.31 (2s, 12H, 4 NCH_3), 3.27 (t, 4H, 2 CH_2), 2.12 (m, 2H, CH_2).

The filtrate was evaporated and the residue was crystallized from toluene to give 5-(4-carboxybutyryl)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **10** (2.10 g, 24%)

R_f 0.66 (CH_2Cl_2/MeOH/AcOH 96:3:1);
FAB MS $C_{11}H_{14}N_2O_6$ (270.24) m/z (%) 293 $[M+Na]^+$ (10), 271 $[M+H]^+$ (100), 253 (76), 225 (22), 211 (20).
^1H NMR ($CDCl_3$) d 17.67 (s, 1H, OH), 3.37, 3.32 (2s, 6H, 2 NCH_3), 3.23 (t, 2H, CH_2), 2.48 (t, 2H, CH_2), 2.05 (m, 2H, CH_2).

Example 12 N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)ethyl] 1-butylamine **2**

5-Acetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (100 mg, 0.50 mmol) was dissolved in n-butylamine (10 ml) and stirred at room temperature overnight. The solvent was evaporated, the residue was washed with ether to give N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)ethyl] 1-butylamine **2** (121 mg, 95%).

R_f 0.33 (EtOAc/hexane 2:1);
FAB MS $C_{12}H_{19}N_3O_3$ (253.28) m/z (%) 266 $[M+Na]^+$ (8), 254 $[M+H]^+$ (100), 195 (14).
^1H NMR ($CDCl_3$) d 12.55 (s, 1H, NH), 3.44 (m, 2H, CH_2), 3.31, 3.30 (2s, 6H, 2 NCH_3), 2.68 (s, 3H, CH_3), 1.69, 1.45 (2m, 4H, 2 CH_2), 0.97 (t, 3H, CH_3).

Example 13 N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] 1-butylamine **4**

A mixture of 5-benzoyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (500 mg, 1.92 mmol) and N,N-diisopropylethylamine (248 mg, 1.92 mmol) in n-butylamine (10 ml) was refluxed for 2 hours. The solvent was evaporated, the residue was washed 1 M $KHSO_4$ solution, dried and evaporated. The residue was washed with ether to give N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] 1-butylamine **4** (575 mg, 95%)

R_f 0.41 (EtOAc/hexane/TFA 10:15:0.1);
FAB MS $C_{17}H_{21}N_3O_3$ (315.36) m/z (%) 338 $[M+Na]^+$ (16), 316 $[M+H]^+$ (100), 307 (14).
^1H NMR ($CDCl_3$) d 12.42 (s, 1H, NH), 7.48 (m, 3H, 3 Ar-H), 7.17 (m, 2H, 2 Ar-H), 3.37, 3.15 (2s, 6H, 2 NCH_3), 3.04 (m, 2H, CH_2), 1.52, 1.32 (2m, 4H, 2 CH_2), 0.86 (t, 3H, CH_3).

Example 14 N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)ethyl] glycine **14**

A mixture of 5-acetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (396 mg, 2.00 mmol), glycine (100 mg, 1.33 mmol) and N,N-diisopropyl-ethylamine (172 mg, 1.33 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml). The resulting suspension was filtered, the precipitate was washed with ether and recrystallized from EtOH giving N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-ethyl] glycine **14** (290 mg, 85%).

R_f 0.28 (CH_2Cl_2/EtOAc/MeOH 10:7:1);
FAB MS $C_{10}H_{13}N_3O_5$ (255.22) m/z (%) 278 $[M+Na]^+$ (15), 256 $[M+H]^+$ (100), 210 (44).
^1H NMR ($CDCl_3$) d 12.58 (s, 1H, NH), 3.64 (s, 2H, CH_2), 3.34, 3.31 (2s, 6H, 2 NCH_3), 2.69 (s, 3H, CH_3).

Example 15 N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] glycine **15**

A mixture of 5-benzoyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (519 mg, 2.00 mmol), glycine (100 mg, 1.33 mmol) and N,N-diisopropylethyl-amine (172 mg, 1.33 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml), dried over $MgSO_4$ and evaporated. The residue was suspended with ether to give N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-phenylmethyl] glycine **15** (360 mg, 86%).

R_f 0.38 (CH_2Cl_2/EtOAc/MeOH 10:7:1);
FAB MS $C_{15}H_{15}N_3O_5$ (317.29) m/z (%) 318 $[M+H]^+$ (60), 272 (15), 130 (100).

^{1}H NMR (DMSO-d_6) d 12.30 (t, 1H, NH), 7.43 (m, 3H, 3 Ar-H), 7.14 (m, 2H, 2 Ar-H), 3.76 (d, 2H, CH_2), 3.20, 2.93 (2s, 6H, 2 NCH_3).

Example 16 N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylethyl] glycine **16**

A mixture of 5-phenylacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione (548 mg, 2.00 mmol), glycine (100 mg, 1.33 mmol) and N,N-diisopropylethyl-amine (172 mg, 1.33 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml), dried over $MgSO_4$ and evaporated. The residue was suspended with ether to give N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylethyl] glycine **16** (360 mg, 81%).

R_f 0.40 (CH_2Cl_2/EtOAc/MeOH 10:7:1);
FAB MS $C_{16}H_{17}N_3O_5$ (331.32) m/z (%) 354 $[M+Na]^+$ (15), 332 $[M+H]^+$ (80), 286 (20), 130 (100).
^{1}H NMR ($CDCl_3$) d 13.05 (s, 1H, NH), 7.32 - 7.16 (m, 5H, 5 Ar-H), 4.69 (s, 2H, CH_2Ar), 4.14 (d, 2H, CH_2), 3.37, 3.29 (2s, 6H, 2 NCH_3).

Example 17 Cleavage of 5-acyl-1,3-dimethylbarbituric acid protected primary amines affording 5-acyl-1,3-dimethylbarbituric acid protected hydroxylamines **34**

N-[1-(1,3-Dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] hydroxylamine **17** and Benzyl 2-deoxy-2-amino-α-D-glucopyranoside **34**
Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxo-pyrimidin-5-ylidene)phenylmethylamino]-α-D-glucopyranoside 22 (100 mg, 0.19 mmol) in NH_2OH/MeOH (20%, 10 ml) was stirred at room temperature for 30 min. The solution was evaporated, the residue was suspended with ether (20 ml)

and filtered to give benzyl 2-deoxy-2-amino-α-D-gluco-pyranoside **34** (45 mg, 90%).

R_f 0.11 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{13}H_{19}NO_5$ (269.28) m/z (%) 292 $[M+Na]^+$ (45), 270 $[M+H]^+$ (100), 253 (20), 178 (18).
^1H NMR (DMSO-d_6) d 7.35 - 7.25 (m, 5H, 5 Ar-H), 4.91, 4.56 (2s, 2H, 2 NH), 4.73 (d, 1H, H-1, $J_{1,2}$= 3.44 Hz), 4.66, 4.40 (2d, 2H, CH_2Ar), 3.61 - 3.05 (5 sugar-H), 2.40 (dd, 1H, H-2).

The filtrate was evaporated and purified by chromatography using CH_2Cl_2/EtOAc/MeOH 10:7:1 to afford N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] hydroxylamine **17** (40 mg, 73%).

R_f 0.76 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{13}H_{14}N_4O_3$ (275.25) m/z (%) 298 $[M+Na]^+$ (13), 276 $[M+H]^+$ (100), 243 (20).
^1H NMR ($CDCl_3$) d 13.95 (s, 1H, NH), 7.32 - 7.16 (m, 5H, 5 Ar-H), 3.39, 3.14 (2s, 6H, 2 NCH_3).

Example 18 N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] acetic hydrazide **18**

A mixture of 5-benzoyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **3** (260 mg, 1.00 mmol) and acetic hydrazide (222 mg, 3.00 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml), dried over $MgSO_4$ and evaporated. The residue was crystallized from MeOH to give N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] acetic hydrazide **18** (250 mg, 79%).

R_f 0.42 (MeCN/$CHCl_3$ 2:1);

FAB MS $C_{15}H_{16}N_4O_4$ (316.31) m/z (%) 339 $[M+Na]^+$ (28), 317 $[M+H]^+$ (100).
^1H NMR ($CDCl_3$) d 13.84 (s, 1H, NH), 7.61 (s,1H, NH), 7.49, 7.20 (2m, 5H, 5 Ar-H), 3.38, 3.13 (2s, 6H, 2 NCH_3), 1.77 (s, 3H, NAc).

Example 19 Cleavage of 5-acyl-1,3-dimethylbarbituric acid protected primary amines affording 5-acyl-1,3-dimethylbarbituric acid protected hydrazines

N-[1-(1,3-Dimethyl-2,4,6(1H,3H,5H)-trioxopyimidin-5-ylidene)phenylmethyl] hydrazine ***19***

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyimidin-5-ylidene)phenylmethyl-amino]-α-D-glucopyranoside **22** (100 mg, 0.19 mmol) in N_2H_4/MeOH (20%, 10 ml) was stirred at room temperature for 30 min. The solution was evaporated, the residue was suspended with ether (20 ml) and filtered to give benzyl 2-deoxy-2-amino-α-D-glucopyranoside **34** (45 mg, 90%).

R_f 0.11 (CH_2Cl_2/EtOAc/MeOH 10:7:3);

The filtrate was evaporated, purified by chromatography using CH_2Cl_2/EtOAc/MeOH 10:7:3 as the mobile phase to give N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] hydrazine **19** (40 mg, 74%).

R_f 0.66 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{13}H_{14}N_4O_3$ (274.25) m/z (%) 297 $[M+Na]^+$ (15), 275 $[M+H]^+$ (100), 243 (20).
^1H NMR ($CDCl_3$) d 13.75 (s, 1H, NH), 7.32 - 7.16 (m, 5H, 5 Ar-H), 3.38, 3.13 (2s, 6H, 2 NCH_3).

Example 20 Cleavage of 5-acyl-1,3-dimethylbarbituric acid protected primary amines with ammonia affording amino-substituted 5-acyl-1,3-dimethylbarbituric acid

5-Benzoimino-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione ***20***

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl-amino]-α-D-glucopyranoside **22** (100 mg, 0.19 mmol) in 10 ml NH_3/MeOH was stirred at room temperature for 30 min. The solution was evaporated, the residue was suspended with ether (20 ml) and filtered to give benzyl 2-deoxy-2-amino-α-D-glucopyranoside **34** (48 mg, 92%).

R_f 0.11 (CH_2Cl_2/EtOAc/MeOH 10:7:3);

The filtrate was evaporated to afford 5-benzo-imino-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **20** (47 mg, 93%).

R_f 0.86 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{13}H_{13}N_3O_3$ (259.25) m/z (%) 282 $[M+Na]^+$ (35), 260 $[M+H]^+$ (100), 243 (20).
^1H NMR ($CDCl_3$) d 12.48 (s, 1H, NH), 7.32 - 7.16 (m, 5H, 5 Ar-H), 3.38, 3.30 (2s, 6H, 2 NCH_3).

Example 21 Cleavage of 5-acyl-1,3-dimethylbarbituric acid protected primary amines with primary amines

N-[1-(1,3-Dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethyl] 1-butylamine ***4***

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6-(1H,3H,5H)-trioxopYrimidin-5-ylidene)phenylmethylamino]-α-D-glucopyranoside **22** (100 mg, 0.19 mmol) in 10 ml n-$BuNH_2$ was stirred at room temperature for 30 min. The solution was evaporated, the residue was suspended with ether

(20 ml) and filtered to give benzyl 2-deoxy-2-amino-α-D-glucopyranoside **34** (48 mg, 92%).

R_f 0.11 (CH_2Cl_2/EtOAc/MeOH 10:7:3);

The filtrate was evaporated to afford N-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-phenylmethyl] 1-butylamine **4** (50 mg, 94%).

R_f 0.89 (CH_2Cl_2/EtOAc/MeOH 10:7:3);

Example 22 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)ethylamino]-α-D-glucopyranoside **21**

A mixture of 5-acetyl-1,3-dimethyl-2,4,6-(1H,3H,5H)-pyrimidinetrione **1** (220 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirring under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml). The resulting suspension was filtered and the precipitate was washed with ether to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6-(1H,3H,5H)-trioxopyrimidin-5-ylidene)-ethylamino]-α-D-glucopyranoside **21** (245 mg, 73%).

R_f 0.43 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{21}H_{27}N_3O_8$ (449.45) m/z (%) 472 $[M+Na]^+$ (12), 450 $[M+H]^+$ (100), 358 (25), 342 (66).
^1H NMR (DMSO-d_6) d 12.68 (d, 1H, NH), 7.46 (d, 2H, 2 Ar-H), 7.31 (m, 3H, 3 Ar-H), 4.95 (d, 1H, H-1, $J_{1,2}$=3.60 Hz), 3.19, 3.15 (2s, 6H, 2 NCH_3), 2.65 (s, 3H, CH_3).

Example 23 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylmethylamino]-α-D-glucopyranoside **22**

A mixture of 5-benzoyl-1,3-dimethyl-2,4,6-(1H,3H,5H)-pyrimidinetrione **3** (290 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was crystallized from MeCN to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-phenylmethylamino]-α-D-glucopyranoside **22** (270 mg, 71%).

R_f 0.35 (CH_2Cl_2/EtOAc/MeOH 10:7:1);
FAB MS $C_{26}H_{29}N_3O_8$ (511.51) m/z (%) 534 $[M+Na]^+$ (18), 512 $[M+H]^+$ (100), 420 (18), 404 (36), 338 (75).
^1H NMR (DMSO-d_6) d 12.47 (d, 1H, NH), 7.41 - 7.17 (m, 10H, 10 Ar-H), 4.66 (d, 1H, H-1, $J_{1,2}$=3.55 Hz), 4.68, 4.48 (2d, 2H, CH_2Ar), 2.99, 2.94 (2s, 6H, 2 NCH_3).

Example 24 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(9-fluorenylmethylamino)]-α-D-glucopyranoside **23**

A mixture of 5-(9-fluorenylcarbonyl)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **5** (388 mg, 1.11 mmol) and benzyl 2-amino-2-deoxy-α-D-glucopyrano-side 34 (200 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was purified by chromatography using $CHCl_3$/MeCN/AcOH 10:10:0.1 to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(9-fluorenylmethylamino)]-α-D-glucopyranoside **23** (140 mg, 31%).

R_f 0.37 ($CHCl_3$/MeCN/AcOH 10:10:0.1);
FAB MS $C_{33}H_{33}N_3O_8$ (599.61) m/z (%) 622 $[M+Na]^+$ (48), 600 $[M+H]^+$ (100), 492 (88), 474 (26), 346 (75).
^1H NMR ($CDCl_3$) d 12.72 (d, 1H, NH), 7.85 - 6.77 (m, 14H, 13 Ar-H, CH), 4.57, 4.22 (2d, 2H, CH_2Ar), 3.47, 3.40 (2s, 6H, 2 NCH_3).

Example 25 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)phenylethylamino]-α-D-glucopyranoside **24**

A mixture of 5-phenylacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **8** (305 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was purified by chromatography using $CHCl_3$/EtOAc/MeOH 10:7:1 as the mobile phase to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-phenylethylamino]-α-D-glucopyranoside **24** (280 mg, 72%).

R_f 0.47 ($CHCl_3$/EtOAc/MeOH 10:7:1);
FAB MS $C_{27}H_{31}N_3O_8$ (525.54) m/z (%) 548 $[M+Na]^+$ (22), 526 $[M+H]^+$ (100), 417 (52), 274 (47).
^1H NMR (DMSO-d_6) d 12.88 (d, 1H, NH), 7.41 - 7.01 (m, 10H, 10 Ar-H), 4.65, 4.39 (2d, 2H, CH_2Ar), 4.38 (d, 1H, H-1, $J_{1,2}$=3.03 Hz), 3.23, 3.09 (2s, 6H, 2 NCH_3).

Example 26 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)diphenylethylamino]-α-D-glucopyranoside **25**

A mixture of 5-diphenylacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **9** (390 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was purified by chromatography using 1,2-dichloroethane-/MeOH/AcOH 10:1:0.1 as the mobile phase to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxo-pyrimidin-5-ylidene)diphenylethylamino]-α-D-glucopyranoside **25** (300 mg, 68%).

R_f 0.37 (1,2-dichloroethane/MeOH/AcOH 10:1:0.1);
FAB MS $C_{33}H_{35}N_3O_8$ (601.63) m/z (%) 624 $[M+Na]^+$ (20), 602 $[M+H]^+$ (100), 494 (47), 348 (42), 338 (39)
^1H NMR ($CDCl_3$) d 13.44 (d, 1H, NH), 8.15 (s, 1H, $CHAr_2$), 7.52 - 6.94 (m, 15H, 15 Ar-H), 4.55, 4.21 (2d, 2H, CH_2Ar), 3.39, 3.29 (2s, 6H, 2 NCH_3).

Example 27 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-(2,2-dimethylpentylamino)]-α-D-glucopyranoside **28**

A mixture of 5-pivaloyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **11** (267 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirring under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was purified by chromatography

using CH_2Cl_2/EtOAc/MeOH 10:7:3 as the mobile phase to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-(2,2-dimethylpentylamino)]-α-D-glucopyranoside **28** (240 mg, 66%).

R_f 0.47 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{24}H_{33}N_3O_8$ (491.52) m/z (%) 514 $[M+Na]^+$ (28), 492 $[M+H]^+$ (100), 270 (25), 240 (54).
^1H NMR ($CDCl_3$) d 12.76 (d, 1H, NH), 7.29 (m, 5H, 5 Ar-H), 4.64, 4.40 (2d, 2H, CH_2Ar), 3.24, 3.21 (2s, 6H, 2 NCH_3), 1.37 (s, 9H, 3 CH_3).

Example 28 Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-(1-adamantylmethylamino)]-α-D-glucopyranoside **29**

A mixture of 5-adamantanecarbonyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **12** (709 mg, 2.23 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (288 mg, 2.23 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was suspended with ether to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)-(1-adamantylmethylamino)]-α-D-glucopyranoside **29** (260 mg, 62%).

R_f 0.45 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{30}H_{39}N_3O_8$ (569.63) m/z (%) 592 $[M+Na]^+$ (60), 570 $[M+H]^+$ (100).
^1H NMR ($CDCl_3$) d 12.74 (d, 1H, NH), 7.33 (m, 5H, 5 Ar-H), 4.65, 4.43 (2d, 2H, CH_2Ar), 3.27, 3.22 (2s, 6H, 2 NCH_3), 2.13, 2.04 (2s, 12H, 6 CH_2), 1.72 (m, 3H, 3 CH).

Example 29 Reaction of primary amines with 5-trichloroacetimino-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)aminomethylamino]-α-D-glucopyranoside ***27***

A mixture of 5-Trichloroacetimino-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **13** (333 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was purified by chromatography using CH_2Cl_2/EtOAc/MeOH 10:7:3 as the mobile phase to give benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)aminomethylamino]-α-D-glucopyranoside **27** (250 mg, 75%).

R_f 0.41 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{20}H_{26}N_4O_8$ (450.44) m/z (%) 473 $[M+Na]^+$ (21), 451 $[M+H]^+$ (100), 358 (15), 342 (74), 265 (269).
^1H NMR (DMSO-d_6) d 10.86 (d, 1H, NH), 10.06 (s, 1H, NH), 7.74 (s, 1H, NH), 7.42 (d, 2H, 2 Ar-H), 7.29 (m, 3H, 3 Ar-H), 4.87 (d, 1H, H-1, $J_{1,2}$= 3.22 Hz), 4.69, 4.48 (2d, 2H, CH_2Ar).

Example 30 Preparation of "Linker-Carbohydrate Conjugate"

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(4-carboxybutylamino)]-α-D-glucopyranoside ***26***

A mixture of 5-(4-carboxybutyryl)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **10** (301 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (240 mg, 1.85 mmol) in abs. EtOH (10 ml) was stirred under reflux

overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml) and washed with 1 M $KHSO_4$ solution (10 ml). The resulting suspension was filtered, the precipitate was washed with ether giving benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(4-carboxybutylamino)]-α-D-glucopyranoside **26** (280 mg, 73%).

R_f 0.28 (CH_2Cl_2/EtOAc/MeOH 10:7:5);
FAB MS $C_{24}H_{31}N_3O_{10}$ (521.51) m/z (%) 544 $[M+Na]^+$ (25), 522 $[M+H]^+$ (100), 430 (21), 414 (75).
^1H NMR (DMSO-d_6) d 12.70 (d, 1H, NH), 7.45 - 7.18 (m, 5H, 5 Ar-H), 4.97 (d, 1H, H-1, $J_{1,2}$=3.47 Hz), 4.97, 4.4.72 (2d, 2H, CH_2Ar), 3.17, 3.14 (2s, 6H, 2 NCH_3), 3.00 (t, 2H, CH_2), 2.34 (m, 4H, 2 CH_2).

Example 31 Chiral 5-acyl-1,3-dimethylbarbituric acid derivatives for primary amine protection

N,N'-Bis-(benzyl 2-deoxy-α-D-glucopyranosid-2-yl)-[5-(2-aminoacetimino)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione] 30 and 5-[N-(benzyl 2-deoxy-α-D-glucopyranosid-2-yl)aminoacetyl]-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **31**

A mixture of 5-chloroacetyl-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **6** (260 mg, 1.11 mmol), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (200 mg, 0.74 mmol) and N,N-diisopropylethylamine (96 mg, 0.74 mmol) in abs. EtOH (10 ml) was stirred under reflux overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (100 ml), washed with 1 M $KHSO_4$ solution (10 ml) and evaporated. The residue was purified by chromatography using CH_2Cl_2/EtOAc/MeOH 10:7:3 as the mobile phase to give N,N'-bis-(benzyl 2-deoxy-α-D-glucopyranosid-2-yl)-[5-(2-aminoacetimino)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione] **30** (110 mg, 21%).

R_f 0.42 (CH_2Cl_2/EtOAc/MeOH 10:7:3);

FAB MS $C_{34}H_{44}N_4O_{13}$ (716.72) m/z (%) 739 $[M+Na]^+$ (22), 717 $[M+H]^+$ (100).
^1H NMR (DMSO-d_6) d 12.58 (d, 1H, NH), 7.43 - 7.25 (m, 10H, 10 Ar-H), 4.65 - 4.24 (4d, 4H, 2 CH_2Ar), 3.18, 3.08 (2s, 6H, 2 NCH_3), and 5-[N-(benzyl 2-deoxy-α-D-glucopyranosid-2-yl)aminoacetyl]-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **30** (80 mg, 23%).

R_f 0.33 (CH_2Cl_2/EtOAc/MeOH 10:7:3);
FAB MS $C_{21}H_{27}N_3O_9$ (465.45) m/z (%) 488 $[M+Na]^+$ (27), 466 $[M+H]^+$ (100).
^1H NMR (DMSO) d 17.22 (s, 1H, OH), 7.41 - 7.27 (m, 5H, 5 Ar-H), 4.68, 4.46 (2d, 2H, CH_2Ar), 3.19, 3.14 (2s, 6H, 2 NCH_3).

Example 32 Preparation of resin-linker-carbohydrate conjugate

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(4-carboxybutylamino)]-3,4,6-tri-O-acetyl-α-D-glucopyranoside - MBHA resin conjugate ***32***

Benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(4-carboxybutylamino)]-α-D-glucopyranoside **26** (300 mg, 1.11 mmol) was dissolved in pyridine (10 ml), cooled to 0°C and acetic anhydride (7 ml) added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the resulting residue was taken up in CH_2Cl_2 (70 ml), washed with 1 M $KHSO_4$ solution, dried over $MgSO_4$ and evaporated. The residue was taken up in DMF (10 ml) and was used as a reagent during the resin work. MBHA resin (Subst. ratio: 0.42 mmol/g) (200 mg) bearing a total amine functionality of 0.084 mmol was swelled in DMF for 20 min. The resin was then washed with fresh DMF and benzyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)(4-carboxybutylamino)]-3,4,6-tri-O-acetyl-α-D-glucopyranoside DMF solution (5 ml, 6.6 equiv.) and N,N'-diisopropylcarbodiimide (88 ml,

6.6 equiv.) were added and the resin gently agitated for 30 min. The TNBS test was faintly positive so using the above conditions, a double coupling was performed, this time producing a negative TNBS test result. The resin was washed with DMF, methanol and finally ether. The resin was then allowed to dry in vacuum over KOH overnight.

Example 33 Carbohydrate deprotection and cleavage of the "fully protected sugar - linker - resin conjugate" providing an "amino substituted resin - linker conjugate" **35**

The resin from Example 32 was gently agitated with sodium methoxide (100 mg, 1.85 mmol) in abs. MeOH (5 ml) at room temperature for 1 h. The resin was washed with abs. MeOH (5x10 ml), DMF(5x10 ml), ether (5x10 ml) and dried under high vacuum for 1 h, giving the resin bonded unprotected benzyl 2-amino-2-deoxy-α-D-glucopyranoside. A sample of resin (5 mg) was cleavaged by saturated NH_3/MeOH (0.2 ml) at room temperature for 10 min. The resin was filtered off, the filtrate was evaporated giving benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** in quantitative yield. During the cleavage conditions the resin was transformed into its amino-substituted form **35**.

Example 34 Preparation of "resin-linker-carbohydrate conjugate" using "amino-substituted resin-linker conjugate"

"Amino-substituted resin-linker conjugate" **35** (100 mg, 0.042 mmol amine functionality), benzyl 2-amino-2-deoxy-α-D-glucopyranoside **34** (34 mg, 0.13 mmol) and diisopropylethylamine (16 mg, 0.126 mmol) in abs. EtOH gently stirred under reflux overnight. The reaction mixture was filtered, the resin was washed with MeOH, DMF, CH_2Cl_2, ether and dried to give the "resin-linker-carbohydrate conjugate" **37**.

Example 35 Preparation of a "hydroxy-substituted resin-linker conjugate" **36**

MBHA resin (Subst. ratio: 0.42 mmol/g) (200 mg) bearing a total amine functionality of 0.084 mmol was swelled in DMF for 20 min. The resin was then washed with fresh DMF and 5-(4-carboxybutyryl)-1,3-dimethyl-2,4,6(1H,3H,5H)-pyrimidinetrione **10** (68 mg, 0.25 mmol) and N,N'-diisopropylcarbodiimide (40 ml, 3.0 equiv.) were added in DMF (5 ml) and the resin gently agitated for 30 min. The TNBS test was faintly positive so using the above conditions, a double coupling was performed, this time producing a negative TNBS test result. The resin was washed with DMF, methanol and finally ether. The resin was then allowed to dry in vacuum over KOH overnight to give **36**.

Example 36 Preparation of a "hydroxy-substituted resin-linker conjugate" using "amino-substituted resin-linker conjugate" **36**

"Amino-substituted resin-linker conjugate" **35** (50 mg, 0.021 mmol amine functionality) was stirred at room temperature in 1 M NaOH solution (2.0 ml) for 10 min. The mixture was filtered, washed with H_2O, methanol and finally ether. The resin was then allowed to dry in vacuum over KOH overnight to give **36**.

Example 37 Preparation of "2-acetyl-1,3-indanedione" **38**

A mixture of 4-dimethylaminopyridine (664 mg, 5.44 mmol), triethylamine (7.6 ml 54.56 mmol), acetic anhydride (6.2 ml, 65.48 mmol in dry 1,2-dichloroethane (60 ml) was stirred at -20°C and a solution of 1,3-indanedione (7.96 g, 54.56 mmol) in 1,2-dichloroethane was added dropwise in 1.5 h. The reaction mixture was stirred for 30 min, then washed with 10% hydrochloric acid (80 ml) and twice with water (80 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was

crystallized from methyl-tert-butylether (50 ml) to give 2-acetyl-1,3-indanedione 38(6.5 g 63%). R_f 0.27 (hexane-ethylacetate-acetic acid 20-5-0.5) MS $C_{11}H_8O_3$ m/z (%) 189 $[M+H]^+$ (100), 166 (72), 104 (20).

Example 38 Methyl2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)ethylamino]-1-thio-b-D-glucopyranoside **39**

Methyl 2-deoxy-2-amino-1-thio-β-D-glucopyranoside (5.00 g, 23.9 mmol) was dissolved in dry ethanol (70 ml) and 1,3-dimethylbarbituric acid (9.47 g, 47.8 mmol) added to form a suspension. Triethylamine (5.40 g, 53.3 mmol) was then added and the resultant clear solution heated at reflux for 14h. The solvent was evaporated, the residue dissolved in dichloromethane (200 ml) and 5% hydrochloric acid solution (200 ml) added. The resultant precipitate was collected and recrystallized from ethyl acetate to yield Methyl 2-deoxy-2-[1-(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)ethylamino]-1-thio-β-D-glucopyranoside **39**, as a colourless solid (7.82 g, 84.1 %)

Rf 0.57 (CH_3CN/H_2O 9:1);
ESI-MS MS m/z 390.0 (M+H);
^1H NMR ($CDCl_3$) d 4.650 (d, 3H, $J_{1,2}$=9.9 Hz, H1), 3.894 (dd, 1H, H-3), 3.716 (dd, 1H, H-4), 3.547 (dd, 1H, H-2), 3.426 (d, 2H, H-6), 3.306 (m, 1H, H-5), 3.266 (s, 6H, 2 x N-CH_3), 2.730 (s, 3H, vinylic-CH_3), 2.211 (s, 3H, *S*-CH_3).

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing

from the scope of the inventive concept disclosed in this specification.

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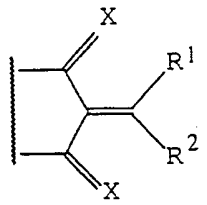
CLAIMS

1. A cyclic compound of general formula I



I

wherein the ring is a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, saturated bicyclo[p,q,r], substituted saturated bicyclo[p, q, r], saturated heterobicyclo[p, q, r], substituted saturated heterobicyclo[p, q, r], unsaturated bicyclo[p, q, r], substituted unsaturated bicyclo[p, q, r], unsaturated heterobicyclo[p, q, r], substituted unsaturated heterobicyclo[p, q, r], saturated tricyclo[p, q, r, s], substituted saturated tricyclo[p, q, r, s,], unsaturated tricycloalkyl[p, q, r, s], unsaturated substituted tricycloalkyl[p, q, r, s], saturated heterotricyclo[p, q, r, s,], substituted saturated heterotricyclo[p, q, r, s,], unsaturated heterotricyclo[p, q, r, s,] and substituted unsaturated heterotricyclo[p, q, r, s,] ring system, where p, q, r and s may be the same or different, and each of p, q, r and s is an integer from 0 to 5;

X is oxygen, sulphur, imino or substituted imino;

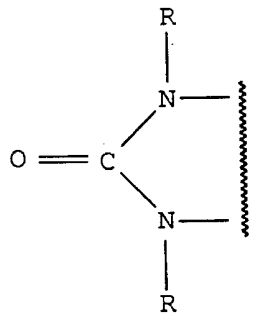
R^1 is hydrogen; an alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloheteroaryl, cycloalkyl, heterocycloalkyl, alkanal, or thioalkanal group, each of which may be substituted or unsubstituted; NH_2, guanidino, CN, substituted amino, quaternary ammonium, O^-, formyl, imino or substituted imino, COOH or a carboxylic acid derivative;

R^2 is an alkylamino, dialkylamino, arylamino, or diarylamino group, each of which may be substituted or unsubstituted; O-substituted hydroxylamino, substituted or unsubstituted hydrazino, substituted or unsubstituted hydrazido, substituted or unsubstituted thiohydrazido, semicarbazido, thiosemicarbazido, OH, O^-M, NH_2, NHOH, SH, S^-M^+, halogen; O-alkyl, O-acyl, O-aryl, alkylthio, S-aryl, acylthio, alkylsulfonyl or arylsulfonyl, each of which may be substituted or unsubstituted; and M is a metal ion, or an organic or inorganic cation such as a quaternary amine group, a trityl group or an ammonium group,

with the proviso that the compound is not one disclosed in International Patent Application No. PCT/AU97/00544.

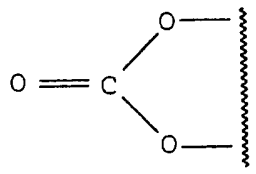
2. A compound according to Claim 1, in which the ring is 4- to 8-membered cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl.

3. A compound according to Claim 1, in which the ring is a 5- to 8-membered ring of the lactone or lactam type, or a 6- to 8-membered ring of the carbamido or substituted carbamido type, as follows:

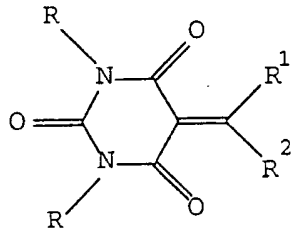


in which each R is independently H, substituted or unsubstituted alkyl, aryl, alkenyl or alkynyl or acyl.

4. A compound according to Claim 1, in which the ring is a 6- to 8-membered ring of the carbonate type, as follows:



5. A compound according to Claim 1 or Claim 2, of general formula II.



II

in which each R is independently H or a substituted or unsubstituted alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or heterocycloalkyl; and

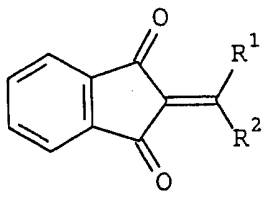
R^1 and R^2 are as defined in Claim 1.

6. A compound according to Claim 5, in which each R group has 1 to 6 carbon atoms.

7. A compound according to Claim 5 or Claim 6, in which each R group has 1 to 4 carbon atoms.

8. A compound according to any one of claims 1 to 3, 5 and 6, selected from the group consisting of 5-acyl-1,3-dimethylbarbituric acid, 6-chloracetyl-1,3-dimethylbarbituric acid, 5-trichloroacetimino-1,3-dimethylbarbituric acid, and derivatives thereof.

9. A compound according to Claim 1 or Claim 2, of general formula III,

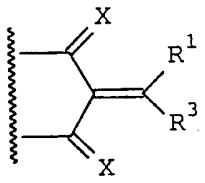


III

in which R^1 and R^2 are as defined in Claim 1.

10. A compound according to any one of Claims 1 to 9, which is chiral.

11. An N-protected compound of general formula IV;



IV

in which the ring, R^1 and X are as defined in any one of Claims 1 to 10, and R^3 is a nitrogen-containing organic compound linked via the nitrogen atom.

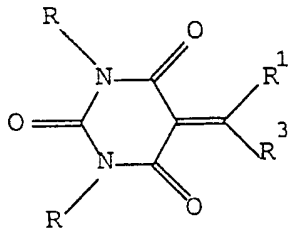
12. A compound according to Claim 11, in which R^3 is an amino sugar, an oligosaccharide, an amino acid or a peptide.

13. A compound according to Claim 11, in which R^3 is a protected, unprotected or substituted sugar amino-, a glycosylamino-, or a glycosylamino group of an oligosaccharide; or a mono- or oligosaccharide coupled through a substituted or unsubstituted alkylamino-, arylamino-, cycloalkylamino, heteroalkylamino, heteroarylamino or heterocycloalkylamino group.

14. A compound according to Claim 11, in which R^3 is an oligosaccharide-O-CH_2-(C_6H_4)-NH-, monosaccharide-O-CH_2-

(C_6H_4)-NH-, oligosaccharide-CO_2CH_2-(C_6H_4)NH-, or monosaccharide-CO_2CH_2-(C_6H_4)-NH group.

15. An N-protected compound of general formula V,



V

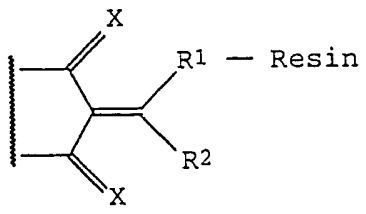
in which R and R^1 are as defined in any one of Claims 5 to 7, and R^3 is a nitrogen-containing organic compound linked via the nitrogen atom.

16. A compound according to Claim 15, in which R^3 is an amino sugar, an oligosaccharide, an amino acid or a peptide.

17. A compound according to Claim 15, in which R^3 is a protected, unprotected or substituted sugar amino-, a glycosylamino-, or a glycosylamino group of an oligosaccharide; or a mono- or oligosaccharide coupled through a substituted or unsubstituted alkylamino-, arylamino-, cycloalkylamino, heteroalkylamino, heteroarylamino or heterocycloalkylamino group.

18. A compound according to Claim 15, in which R^3 is an oligosaccharide-O-CH_2-(C_6H_4)-NH-, monosaccharide-O-CH_2-(C_6H_4)-NH-, oligosaccharide-CO_2CH_2-(C_6H_4)NH-, or monosaccharide-CO_2CH_2-(C_6H_4)-NH group.

19. A support of general formula VI for solid-phase synthesis of oligosaccharides, peptides or organic compounds, comprising a resin and a linker covalently attached to the resin:

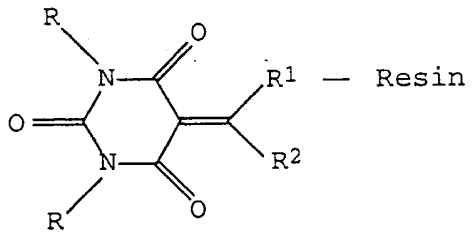


VI

wherein the ring, X and R^2 are as defined in any one of Claims 1 to 10, and

R^1 is a substituted or unsubstituted alkyl, cycloalkyl, heteroalkyl, heteroaryl, heterocycloalkyl or carboxylamido spacer group which is directly coupled to the resin support, or which may optionally be coupled to the resin support via a suitable covalent linkage, which is stable to conditions of oligosaccharide synthesis and cleavage.

20. A support according to Claim 19, in which the linker is a barbituric acid of general formula VII



VII

wherein R and R^2 are as defined in any one of Claims 5 to 7, and

R^1 is a substituted or unsubstituted alkyl, cycloalkyl, heteroalkyl, heteroaryl, heterocycloalkyl or carboxylamido spacer group which is directly coupled to the resin support, or which may optionally be coupled to the resin support via a suitable covalent linkage which is stable to conditions of oligosaccharide synthesis and cleavage.

21. A compound according to Claim 19 or Claim 20, in which the covalent linkage is provided by a -CONH-, -O-, -S-, -NH-, -COO-, -COS-, -CH=N-, -NHCONH-, -NHCSNH or -NHNH- grouping.

22. A support according to any one of Claims 19 to 21, in which the resin swells in water and/or in an organic solvent, and which comprises one of the following substituents: halogen, hydroxy, carboxyl, SH, NH_2, formyl, SO_2NH_2, or $NHNH_2$.

23. A method of solid-phase synthesis of oligosaccharides, comprising the step of sequentially linking mono- or oligosaccharide groups to a support according to any one of Claims 19 to 22.

24. A method according to Claim 23, in which

a) the linker is synthesised directly on the resin in a stepwise manner prior to the coupling of the initial sugar group, or

b) the linker-initial sugar conjugate is synthesised in solution phase and subsequently coupled to the solid support, with subsequent sugars being sequentially attached.

25. A method according to Claim 23 or Claim 24, in which the support comprises a resin, a linker and a saccharide selected from the group consisting of monosaccharides, oligosaccharides, aminosaccharides and aminooligosaccharides.

26. A method according to any one of Claims 23 to 25, in which the second and all subsequent sugar groups are coupled to the oligosaccharide chain-resin conjugate after the last sugar in the oligosaccharide chain is partially deprotected.

27. A method according to any one of Claims 23 to 26, in which the first sugar attached to the resin-linker unit is an unprotected, partially protected or fully protected glycoside, aminoglycoside, ether-linked sugar, or amino-linked sugar.

28. A method according to Claim 27, in which the first sugar coupled to the resin is an aminosugar, an aminoglycoside or an amino-oligosaccharide, or a glycosyl amine of an oligosaccharide.

29. A method according to any one of Claims 23 to 28, in which the oligosaccharide is branched, and deprotection is achieved by using one or more protecting groups selected from the group consisting of acyl-type, trityl, methoxytrityl, methoxybenzyl, silyl and photolabile protecting groups in addition to permanent ether-type protecting groups.

30. A reagent for solution phase synthesis of sugar-containing compounds, comprising a barbituric acid derivative compound according to any one of Claims 5 to 8 or any one of Claims 15 to 18.

31. A linker-saccharide complex, comprising a linker group and a protected saccharide compound according to any one of Claims 11 to 18.

32. A method of solution phase synthesis of oligosaccharides, comprising the step of sequentially linking mono- or oligosaccharide groups to a compound according to any one of Claims 13, 14, 17, 18 or 31.

33. A method according to Claim 32, in which combinatorial synthesis of aminoglycosides is performed.

34. A kit useful in solid phase synthesis or combinatorial synthesis, comprising

a) a resin-linker-saccharide, resin-linker-peptide, or resin-linker-amino acid-support according to any one of Claims 19 to 22,

b) a linker-saccharide, linker-aminosugar, linker-peptide, or linker-amino acid complex according to any one of Claims 11 to 18, or

c) a resin-linker support complex according to any one of Claims 19 to 22,

and optionally also comprising one or more further reagents such as protecting agents, deprotecting

agents, and/or solvents suitable for solid phase or combinatorial synthesis.

35. A kit for solution phase synthesis or combinatorial synthesis of oligosaccharides, comprising a compound according to any one of Claims 13, 14, 17, 18 or 31, and optionally also comprising one or more further reagents such as protecting agents, deprotecting agents, and/or solvents suitable for solid phase or combinatorial synthesis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00808

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07D 239/62; C07H 001/00, 005/06, 015/18, 015/26; C08J 007/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
-

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN, File Reg, File CA, Substructure search.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	AU, A 38422/97 (Alchemia Pty. Ltd.), 5 March 1998. See whole document.	11-14, 19, 21-29, 31-35
X	J. Am. Chem. Soc., 1994, 116, 7415-7416, B.W.Bycroft *et al.*, "Synthesis of the Spider Toxins Nephilatoxin-9 and -11 by a Novel Solid - Phase Strategy". See compounds (4) and (5) and Dde-OH.	1, 2, 11, 13, 34, 35

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1998	17 NOV 1998
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **L.F. McCAFFERY** Telephone No.: (02) 6283 2573

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00808

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Chem. Soc. Chem. Commun., 1995, 2209, W.C. Chan *et al.* "A Novel 4- Aminobenzyl Ester-based Carboxy-protecting Group for Synthesis of Atypical Peptides by Fmoc-Bu^t Solid-Phase Chemistry." See compounds 1 to 6	1, 2, 11, 13, 14, 34, 35
X	J. Chem. Soc. Chem. Commun., 1993, 778, B.W. Bycroft *et al.* "A novel Lysine-protecting Procedure for Continous Flow Solid Phase Synthesis of Branched Peptides." See compounds 1 to 3	1, 2, 11, 12, 34, 35
X	Chemical Abstracts 126: 8618 and Pept. 1994, Proc Eur. Pept. Symp., (1995), W.C. Chan *et al.*, "Novel protecting group for Fmoc/tBu solid-phase synthesis of side chain carboxy modified peptides". See Abstract	1, 2, 11, 12, 34, 35
X	Chemical Abstracts 124: 202402 and Org. Prep. Proced. Int., 1995, 27(6) 625-635, F. Palacios *et al.*, "1, 3-Dipolar cycloaddition of azidoalkyl phosphonates and -carboxylates to maleimide and naphthoquinone". See Abstract	1, 2, 9 to 12, 34, 35
X	Chemical Abstracts 109:211406 and J. Chem. Soc. Perkin Trans. I, 1988, 3, 541-544, R.Grigg *et al.*, "X:Y-ZH systems as potential 1, 3-dipoles Part 9." See Abstract	1, 2, 9to12, 34, 35
X	Chemical Abstracts 92: 215102 and Latv. PSR Zinat. Akad. Vestis., Kim. Ser., 1979, 6, 713-16, E. Gudriniece *et al.*, "2-Aminomethylene-1, 3-indandione and its reactions with amino acids". See Abstract	1, 2, 9 to 12, 34, 35
X	Chemical Abstracts 114: 23660 and Latv. PSR Zinat. Akad. Vestis, Kim. Ser., 1990, 4, 445-453, M. Jure *et al.*, "Synthesis and Cytokine activity of some 6-methinoaminopurine derivatives". See Abstract	11, 13, 34, 35
P,X	WO98/14429 (Chemipro Kasei Kaisha, Ltd), 9 April 1998 See whole document	1-8, 11, 15, 34,35
P,X	WO 98/38197 (Alchemia Pty Ltd), 3 September 1998 See whole document	1, 2, 11-14, 19, 21-29, 31-35
X	Eur. J. Med. Chem.-Chimica Therapeutica, March-April, 1978, 13(2), 155-160, G.Alonso *et al.*, "Cytostatic quinones. II. Synthesis of N-glycosyl heterocyclic quinones". See compounds 5a and 5b.	1, 2, 9 to 13, 31, 34, 35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00808

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1 to 11, 15 and 19 are so broad in scope that a search could not be carried out on economic grounds. Indeed a relatively narrow substructure search of indene and barbituric acid type derivatives resulted in several hundred compounds falling within the scope of the above claims. Accordingly this search report has been limited largely to the invention(s) defined by Claims 12 to 14, 16 to 18 and 19 to 35.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 98/00808

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
AU	38422/97	WO	9808799
WO	9814423	AU	43986/97

END OF ANNEX